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VIEWPOINT
Heart failure and cardiomyopathies

Heart failure with preserved ejection fraction: underdiagnosed and undertreated in patients with tricuspid regurgitation

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Tricuspid regurgitation (TR) has long been an under-recognized valvular disorder, which is prevalent in ~70 million people worldwide and is independently associated with an increased risk of all-cause and cardiovascular mortality.[1] Historically, treatment options for TR have been limited, but various transcatheter TR interventions have recently emerged as promising therapies for patients with severe TR.[2,3] Tricuspid regurgitation is categorized as primary, lead-related, or secondary, with the latter group comprising the majority of the overall disease prevalence (70%–80%). Secondary TR is classified into (i) ventricular functional TR characterized as dilation of tricuspid annulus with tethering of the tricuspid valve due to right ventricular dysfunction (ventricular functional TR) commonly caused by left heart disease [e.g. heart failure (HF) with reduced ejection fraction (HFrEF) and pulmonary hypertension] and (ii) atrial functional TR characterized as dilation of tricuspid annulus caused by right atrial dilatation without right ventricular dysfunction.[4] Atrial functional TR has long been poorly defined due to a perceived absence of a clear aetiology and has been previously characterized as idiopathic or isolated.[5] More recently, it has emerged as a critical phenotype associated with long-standing atrial fibrillation and HF with preserved ejection fraction (HFpEF).[6]

TR is common in patients with HF; it affects up to 50% of patients with HF and is associated with a higher symptomatic burden and worse clinical outcomes.[7] Although TR can co-exist with either HF phenotype, several studies have reported a stronger association between HFpEF and TR compared with HFrEF.[8] Data from the ESC-HFA EORP (European Society of Cardiology Heart Failure Association EURObservational Research Programme) registry reported that HF patients with isolated TR were more likely to have HFpEF than HFrEF and had a higher risk of all-cause death compared with patients with isolated mitral regurgitation or combined mitral regurgitation and TR.[8] This association is biologically plausible given the epidemiological, clinical, and mechanistic overlap of TR and HFpEF.[6] Both TR and HFpEF are more prevalent in women and in the elderly and are associated with long-standing atrial fibrillation and left atrial enlargement (*Graphical Abstract*, *Panel A*).

The presence of severe TR has also been found to be predictive of HFpEF, with up to 90% of patients with severe TR having clinically manifest HFpEF.[9] Notably, TR in patients with HFpEF does not necessarily occur in the presence of right ventricular dysfunction. An observational study of 328 patients with HFpEF reported that in the 21% of patients with severe TR, only one-third had evidence of right ventricular dilation.[10] It is likely that TR in HFpEF lies on a pathophysiological spectrum, with TR being a consequence or a cause of HFpEF. First, TR may be a direct consequence of elevated left-sided pressures and post-capillary pulmonary hypertension in HFpEF resulting in ventricular functional TR. Second, TR may co-exist with HFpEF and occur as atrial functional TR due to right atrial myopathy with or without long-standing atrial fibrillation (only 38% of atrial functional TR have atrial fibrillation); this may lead to ventricular remodelling with tricuspid leaflet tethering related to either HFpEF or TR (or both) leading to right ventricular dysfunction. Third, TR is associated with HFpEF with latent pulmonary disease, whereby an increase in pulmonary vascular resistance is observed during exercise, which appears to unmask underlying TR and its haemodynamic effects.[11] Fourth, severe TR may lead to right ventricular dilation causing bulging of the ventricular septum into the left ventricle (ventricular interdependence) leading to impairment of left ventricular diastolic filling and resultant HFpEF (*Graphical Abstract*, *Panel B*). These different mechanisms are not necessarily mutually exclusive and may be present concurrently in the same patient.

These data strongly suggest the possibility of HFpEF masquerading as TR. This is important as HFpEF is difficult to diagnose, and until recently, there were not many therapeutic options for these patients. There have been recent breakthroughs of novel therapies for HFpEF, however, including sodium-glucose cotransporter-2 (SGLT-2) inhibitors as well as glucagon-like peptide-1 receptor agonists in obese HFpEF patients that have shown to improve outcomes, SGLT-2 inhibitors have been shown to decrease pulmonary artery pressures in patients with HF across the spectrum of left ventricular ejection fraction.[12] It is possible that SGLT-2 inhibitors may lessen TR severity and improve clinical outcomes in patients with HFpEF. However, SGLT-2 inhibitors and other HF therapies have not been systematically evaluated for their effect on TR severity. Moreover, patients with severe valvular disease, including TR, were excluded from clinical trials of SGLT-2 inhibitors in

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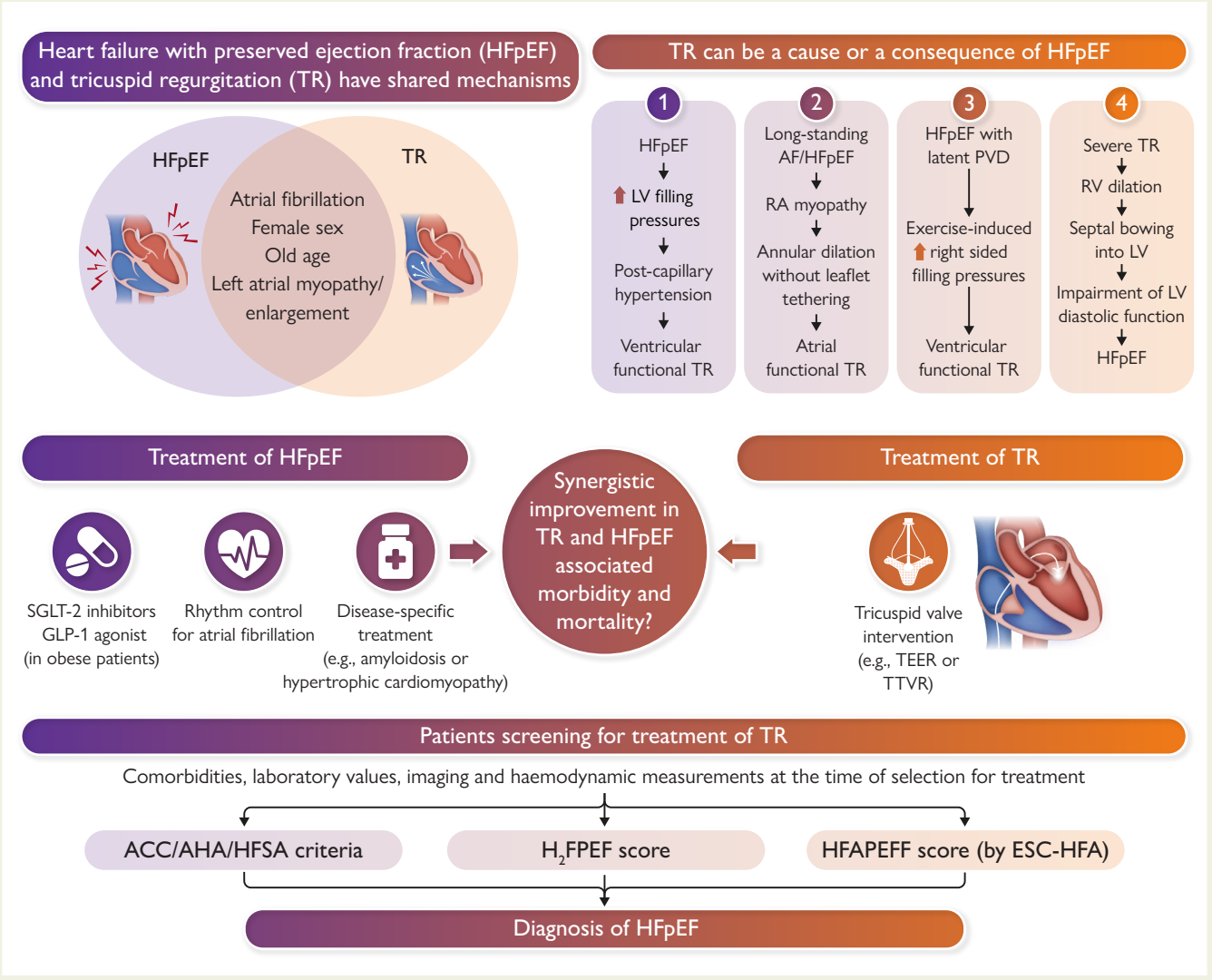
Graphical Abstract



An illustration of the risk factors, clinical features, possible mechanisms, and management of tricuspid regurgitation and heart failure with preserved ejection fraction (*A–C*). An algorithm outlining the application of validated diagnostic criteria of heart failure with preserved ejection fraction amongst patients with tricuspid regurgitation (*D*). ACC/AHA/HFSA, American College of Cardiology/American Heart Association/Heart Failure Society of America; BMI, body mass index; ESC-HFA, European Society of Cardiology - Heart Failure Association; GLP-1, glucagon-like peptide 1; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PVD, pulmonary vascular disease; RA, right atrium; RV, right ventricle; SGLT-2, sodium-glucose cotransporter-2; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TTVR: transcatheter tricuspid valve replacement.

HFpEF. Managing congestion and pulmonary artery pressures via implantable pulmonary pressure sensors improves outcomes in patients with HFpEF. Novel therapies have also been successfully developed for subgroups of HFpEF patients, including amyloidosis or hypertrophic cardiomyopathy. Catheter ablation for atrial fibrillation, which is a major risk factor for both TR and HFpEF, is also associated with an improvement in both TR severity and diastolic dysfunction in HFpEF. It is highly suggestive that implementation of current medical therapy in HFpEF, use of disease-specific therapies, and achieving long-term rhythm control in co-existent atrial fibrillation in the presence of mild to moderate TR could prevent the development of severe TR and improve outcomes in HFpEF (*Graphical Abstract*, *Panel C*). The American College of Cardiology, American Heart Association, and Heart Failure Society of America (ACC/AHA/HFSA) also give a Class II recommendation for the use of renin–angiotensin system modulators and mineralocorticoid receptor antagonists in these patients, whereas the European Society of Cardiology does not provide a specific recommendation.

Transcatheter TR interventions [including transcatheter edge-to-edge-repair (TEER)] are associated with favourable haemodynamic changes and myocardial remodelling that could potentially improve outcomes in patients with HFpEF.[13] One may argue that improvement in TR may lead to an increase in left ventricular filling pressures resulting in worsening diastolic dysfunction, and procedural success has been found to be lower in patients with increased right-sided filling pressure.[14] However, in a single-arm study of 20 patients evaluating the feasibility and haemodynamic effects of TEER in patients with HFpEF, a reduction in TR was associated with normalization of impaired left

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ventricular–right ventricular interaction and an improvement in left ventricular diastolic function.[15]

Based on their intertwined pathophysiology, it should be noted that in the presence of underlying HFpEF and atrial fibrillation (with or without HFpEF), the effect of transcatheter TR intervention may be attenuated. Similarly, treatment of HFpEF or atrial fibrillation may not be as effective if the patient has untreated concomitant TR. Hence, it is likely that transcatheter TR interventions in conjunction with other HFpEF therapies like SGLT-2 inhibitors and rhythm control for atrial fibrillation would lead to improvement in TR outcomes. Although patients enrolled in the Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal (TRILUMINATE) were on reasonable medical therapy for HF, SGLT-2 inhibitor use was limited as it was not established as a Class 1 indication for HFpEF during the enrolment period. Moreover, the lack of a significant effect on outcomes in the TRILUMINATE trial may be related to underlying undiagnosed and untreated HFpEF, which may represent a cohort that may deserve other specific treatments in addition to transcatheter TR interventions. These data suggest the potential of not only improving outcomes of HFpEF in patients undergoing transcatheter TR interventions but also reducing the risk of developing symptomatic HFpEF in those with latent subclinical abnormalities (*Graphical Abstract*, *Panel C*).

While the clinical trials in patients with TR using novel percutaneous techniques have been encouraging, these trials did not systematically evaluate HFpEF at baseline. This has significant consequences.

(1) We do not know what proportion of patients in the clinical trials had an important comorbidity.
(2) We do not know if effective diagnosis and treatment of HFpEF could reduce the need for TR intervention.
(3) If HFpEF is treated effectively prior to transcatheter TR intervention, would it improve the outcomes of the interventions considering the potential of less haemodynamic challenge to the valvular procedure?
(4) For patients intolerant to medical therapy, can transcatheter TR interventions help enable more effective medical HF treatment?
(5) Can transcatheter TR interventions prevent the development of clinical HFpEF?
(6) Can transcatheter TR interventions improve HFpEF outcomes?

Mitigating these concerns can potentially have a major impact on patient-centered outcomes and procedural success but have been unaddressed in clinical trials evaluating TR interventions. We urge that, as best as possible, there should be a retrospective assessment of HFpEF in existing data from trials in patients with TR based on baseline history, examination, natriuretic peptide levels, and haemodynamic data from right heart catheterization. There are several validated diagnostic criteria including the AHA/ACC/HFSA criteria, H2FPEF score, and the HFA-PEFF that can be applied to patients at enrolment of clinical trials or retrospectively using trial/registry data to establish HFpEF diagnosis amongst patients with TR (*Graphical Abstract*, *Panel D*). Importantly, future trials in patients with TR should systematically evaluate HFpEF at baseline, characterize and phenotype these patients, effectively treat them before enrolment, and post-intervention, monitor both procedural related outcomes and those related to underlying HFpEF in patients with prevalent disease at baseline. New-onset clinically manifest HFpEF in those without HFpEF diagnosis at baseline should be assessed as a secondary endpoint in these patients as well.

Declarations

Disclosure of Interest

K.M.T. has nothing to disclose. M.M. has received consulting fees from Abbott Vascular, Actelion, Amgen, AstraZeneca, Bayer, Edwards Therapeutics, LivaNova, Servier, Vifor Pharma, and WindTree Therapeutics. J.B. is a consultant to Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, CardioCell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, PharmaIN, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll.

References

1. Wang N, Fulcher J, Abeysuriya N, McGrady M, Wilcox I, Celermajer D, *et al.* Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2019;**40**:476–84. https://doi.org/10.1093/eurheartj/ehy641
2. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, *et al.* Transcatheter repair for patients with tricuspid regurgitation. *N Engl J Med* 2023;**388**:1833–42. https://doi.org/10.1056/NEJMoa2300525
3. Kodali S, Hahn RT, Makkar R, Makar M, Davidson CJ, Puthumana JJ, *et al.* Transfemoral tricuspid valve replacement and one-year outcomes: the TRISCEND study. *Eur Heart J* 2023;**44**:4862–73. https://doi.org/10.1093/eurheartj/ehad667
4. Muraru D, Badano LP, Hahn RT, Lang RM, Delgado V, Wunderlich NC, *et al.* Atrial secondary tricuspid regurgitation: pathophysiology, definition, diagnosis, and treatment. *Eur Heart J* 2024;**45**:895–911. https://doi.org/10.1093/eurheartj/ehae088
5. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, *et al.* Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;**7**:1185–94. https://doi.org/10.1016/j.jcmg.2014.07.018
6. Packer M, Lam CSP, Lund LH, Redfield MM. Interdependence of atrial fibrillation and heart failure with a preserved ejection fraction reflects a common underlying atrial and ventricular myopathy. *Circulation* 2020;**141**:4–6. https://doi.org/10.1161/CIRCULATIONAHA.119.042996
7. Bartko PE, Hülsmann M, Hung J, Pavo N, Levine RA, Pibarot P, *et al.* Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. *Eur Heart J* 2020;**41**:2799–810. https://doi.org/10.1093/eurheartj/ehaa129
8. Adamo M, Chioncel O, Benson L, Shahim B, Crespo-Leiro MG, Anker SD, *et al.* Prevalence, clinical characteristics and outcomes of heart failure patients with or without isolated or combined mitral and tricuspid regurgitation: an analysis from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail* 2023;**25**:1061–71. https://doi.org/10.1002/ejhf.2929
9. Naser JA, Lee E, Scott CG, Kennedy AM, Pellikka PA, Lin G, *et al.* Prevalence and incidence of diastolic dysfunction in atrial fibrillation: clinical implications. *Eur Heart J* 2023;**44**:5049–60. https://doi.org/10.1093/eurheartj/ehad592
10. Harada T, Obokata M, Omote K, Iwano H, Ikoma T, Okada K, *et al.* Functional tricuspid regurgitation and right atrial remodeling in heart failure with preserved ejection fraction. *Am J Cardiol* 2022;**162**:129–35. https://doi.org/10.1016/j.amjcard.2021.09.021
11. Caravita S, Baratto C, Filippo A, Soranna D, Dewachter C, Zambon A, *et al.* Shedding light on latent pulmonary vascular disease in heart failure with preserved ejection fraction. *Heart Fail* 2023;**11**:1427–38. https://doi.org/10.1016/j.jchf.2023.03.003
12. Nassif ME, Qintar M, Windsor SL, Jermyn R, Shavelle DM, Tang F, *et al.* Empagliflozin effects on pulmonary artery pressure in patients with heart failure. *Circulation* 2021;**143**:1673–86. https://doi.org/10.1161/CIRCULATIONAHA.120.052503
13. Bourcier TB, Raoult TR, Benard TB, Willoteaux SW, Pinaud FP, Prunier FP, *et al.* Cardiac remodeling after tricuspid transcatheter edge-to-edge repair: from the right to the left ventricle. *Archives of Cardiovascular Diseases Supplements* 2023;**15**:269. https://doi.org/10.1016/j.acvdsp.2023.04.054
14. Rommel KP, Bonnet G, Fortmeier V, Stolz L, Schöber AR, von Stein J, *et al.* Congestion patterns in severe tricuspid regurgitation and transcatheter treatment: insights from a multicentre registry. *Eur J Heart Fail* 2024;**26**:1004–14. https://doi.org/10.1002/ejhf.3235
15. Kresoja KP, Rosch S, Schöber AR, Fengler K, Schlotter F, Bombace S, *et al.* Implications of tricuspid regurgitation and right ventricular volume overload in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2024;**26**:1025–35. https://doi.org/10.1002/ejhf.3195

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